European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT
FOR
Telmisartan teva

International Nonproprietary Name:
Telmisartan

Procedure No. EMEA/H/C/001146

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 06 March 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Telmisartan Teva, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The application concerns a generic medicinal product as defined in Article 10(1) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength(s), pharmaceutical form(s): **Micardis 20 mg, 40 mg and 80 mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- Date of authorisation: **1998/12/16**
- Marketing authorisation granted by: **Community**
- Marketing authorisation number(s): **EU/1/98/090/009-012,**
  EU/1/98/090/001-004, 013, 015, 017, 019,
  EU/1/98/090/005-008, 014, 016, 018, 020

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength(s), pharmaceutical form(s): **Micardis 80 mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- Date of authorisation: **16/12/1998**
- Marketing authorisation(s) granted by: **Community**
- Marketing authorisation number(s): **EU/1/98/090/005-008 and 014, 016, 018, 020**
- Bioavailability study(ies) reference number(s)/EudraCT number(s): **Protocol XX019**

The Rapporteur appointed by the CHMP and the evaluation team was: Prof. János Borvendég.

Scientific Advise:

The Applicant did not seek Scientific Advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 06 March 2009
- The procedure started on 25 March 2009
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2009.
- During the meeting on 20-23 July 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 September 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 October 2009.
- The applicant submitted additional minor clarifications on 09 November 2009.
- The Rapporteur circulated a revised Assessment Report to all CHMP members on 16 November 2009.
- During the meeting on 16-19 November 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Telmisartan Teva on 19 November 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Telmisartan Teva 20, 40 and 80 mg is a generic medicinal product containing telmisartan as the active substance.
Telmisartan is indicated for the treatment of essential hypertension in adults. Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykin in mediated adverse effects.

The efficacy and safety of telmisartan has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference product Micardis.

The indication proposed for Telmisartan Teva is the same as the authorised indication for the reference medicinal product.

2.2 Quality aspects

Introduction

Telmisartan Teva is presented as immediate release tablets, containing 20, 40 and 80mg of telmisartan as the active substance.
Other ingredients include microcrystalline cellulose, sodium starch glycolate, poloxamer 188, meglumine, povidone (PVP K-30), sorbitol and magnesium stearate. All strengths have the same proportional composition.
The tablets are packaged in Alu-Alu blister packs.

Active Substance

The active substance is telmisartan, a well known active substance described in Ph. Eur. (Ph.Eur monograph number: 2154). Its chemical name is 4'-[(1,4'-Dimethyl-2'-propyl[2,6'-bi-lH-benzimidazoll-l'-yl)methyl][l,l'-biphenyl]-2-carboxylic acid.
It is a white to slightly yellowish coloured powder, practically insoluble in water, but freely soluble in organic solvents. Telmisartan has no chiral centers and exhibits no stereoisomerism. The chemical structure of the molecule has been established by spectral (UV, IR, ^{1}H and ^{13}C NMR and mass spectra) elemental and thermal (DSC) analyses. The active substance exhibits polymorphism. The capability of the analytical methods used to discriminate the potential polymorphs has been demonstrated and batch analysis data confirm that the manufacturing process used consistently produces the same polymorphic form.
An Active Substance Master File has been provided in support of this application from the active substance manufacturer.

- Manufacture

The active substance is synthesised using commercially available starting materials. The process is adequately described and satisfactory specifications have been set for reagents, solvents and auxiliary

materials used in the process. All critical in-process controls parameters are well established and justified.

A reasoned discussion on impurities arising from the starting materials, the route of synthesis and on degradation products has been provided. All impurities are controlled in the final active substance specification in accordance with the Ph. Eur. requirements. An in-house process related impurity (intermediate) is also controlled in the active substance specification. The residual solvents are also controlled at the specifications in accordance with ICH Q3C.

Appropriate information of packaging materials for Telmisartan active substance has been described. Specifications and analytical reports for the packaging components have been presented and the suitability of the container closure system of the active substance for use with food and pharmaceuticals has been confirmed.

- Specification

The specification of telmisartan was set to be in line with the current Ph. Eur. monograph and the ICH guidelines. The active substance specification includes tests for appearance, assay (HPLC), identification (IR), solubility, related substances (by HPLC), X-ray powder diffraction pattern, loss on drying and sulphated ash. In addition the finished product manufacturer is testing for residual solvents (by GC), and particle size distribution. The non-compendial analytical methods have been appropriately validated.

Batch analysis data from five batches have been provided. The results confirm batch-to-batch consistency and compliance to the Ph. Eur. monograph and the additional specifications.

- Stability

Data from stability studies on three production scale batches have been provided. Samples were stored for up to 36 months at long term conditions (25°C/60% RH) and for 6 months at accelerated conditions (40°C/75% RH) in accordance with ICH requirements. All batches have been tested for conformance with the specifications using stability indicating analytical methods. In all cases the batch analysis data met the predefined specifications and no significant trends were observed.
In addition stability data have been provided under stress conditions (heat, acid hydrolysis, base hydrolysis, photo degradation, water hydrolysis and hydrogen peroxide treatment).
The presented stability data support the assigned retest period of 36 months for telmisartan with no special storage conditions, when packaged in the packaging material described.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substance and exhibiting the same bioavailability as the reference product Micardis® tablets marketed by Boehringer Ingelheim, in order to comply with the regulations pertaining to abridged applications in the European Union.
A common formulation was developed for Telmisartan 20, 40 and 80 mg tablets that is proportional for each strength. Most of the excipients of Teva's products are common to the reference product except that Telmisartan Teva does not contain sodium hydroxide, and Micardis tablets do not contain poloxamers (Lutrol F68, Poloxamer 188) and cellulose microcrystalline (Avicel PH-102).
The manufacturing process is common for all strengths.
The bioequivalence study was performed using *Telmisartan TEVA 80 mg tablets (batch K-36856)* versus *Micardis® 80 mg tablets (batch number 706944*, marketed in Germany). It is acceptable to rely on the 80 mg bioequivalence study also for the 20 mg and 40 mg strengths for the following reasons:

- the pharmaceutical products of different strengths are manufactured at the same site by the same manufacturer and manufacturing process,
- the qualitative composition of the different strengths are the same,

- the composition of the strengths are proportional,
- Although there is no linear relationship between doses and plasma levels Cmax over the dose range of 20–160 mg, there is no evidence of clinically relevant accumulation of the active substance taken at the recommended dose. Therefore the selection of the 80 mg dose to establish bioequivalence is acceptable, in line with the Questions and Answers on the Bioavailability and Bioequivalence guideline (EMEA/CHMP/EWP/40326/2006): a single strength study may be acceptable if the study is conducted on the highest dose for drugs with a demonstrated greater than proportional increase in AUC or Cmax with increasing dose during single or multiple dose studies.
- Appropriate in vitro dissolution data has been provided to confirm the adequacy of waiving additional in vivo bioequivalence testing.

The dissolution test design has been extensively discussed and has been found adequate based on data from solubility tests of the active substance and similarity tests for the new and reference products in different pH media. The discriminatory nature of the dissolution method has also been satisfactorily demonstrated.

- Manufacture of the Product

The manufacturing process is a standard process.
All critical process parameters have been identified and controlled by appropriate in process controls. Validation data from pilot scale batches demonstrate that the process is capable, reproducible and provides a product that complies with the in-process and finished product specifications. The validation protocol for the production scale batches had been adequately described.

- Product Specification

The finished product specification includes tests for description, appearance, identification, assay (HPLC), dissolution, content uniformity (Ph. Eur.), friability (Ph. Eur.), thickness, resistance to crushing (Ph. Eur.), impurities and degradation products (HPLC), microbial count and water content.

Batch analysis data from two production scale batches for each strength have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Data from stability studies on two stability batches for each strength have been provided. Samples were stored for up to 12 months at long-term conditions (25°C/60% RH) and for 6 months at accelerated conditions (40°C/75% RH) in accordance with ICH requirements. All batches have been tested for physical and technological (appearance, dissolution), chemical (assay, degradation products) and microbiological parameters using stability indicating methods. In all cases the parameters tested remained within the proposed specifications and no significant trends were observed.
The results of photostability studies show that the finished product is not sensitive to light.
As a conclusion the proposed shelf-life has been sufficiently supported by the stability studies performed.

Discussion on chemical, pharmaceutical, and biological aspects.

The quality of Telmisartan Teva is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well known and has is described in a Ph. Eur. monograph. The quality of the active substance is regarded to be suitable for the intended use and appropriately controlled by the applicant. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing

process of the finished product has been adequately described and controlled with appropriate in process controls. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.
In comparison with the EU reference product, Telmisartan Teva has been shown to have the same qualitative and quantitative composition in terms of the active substance. The excipients used are mostly the same with some minor modifications. Both the EU reference product and Telmisartan Teva exhibit similar dissolution profiles.

2.3 Non-Clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of telmisartan are well known. As telmisartan is widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The Nonclinical Overview is based on literature searches including several databases as Medline and Toxline and information available via the US Freedom of Information Act (FDA 1998). The Nonclinical Overview refers to 18 publications up to year 2008.

The environmental risk assessment (ERA) in line with the CHMP Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00) was not submitted; however, a justification for omission of environmental risk assessment was provided. This was based on the fact the generic medicinal product is intended to substitute the reference product and it will not result in additional hazard to the environment. The supplied justification for the lack of a full ERA was considered acceptable by the CHMP.

Pharmacology

In vitro, AT1 receptor antagonists inhibit the contractile effects of AII in all vascular smooth muscle preparations. In vivo, they prevent and reverse all the known effects of AII including: rapid pressure response; slow pressure response; stimulatory effects on the peripheral sympathetic nervous system; CNS effects such as thirst, vasopressin release and sympathetic tone; release of adrenal catecholamines; secretion of aldosterone; direct and indirect effects of AII on the kidneys; growth-promoting actions. Furthermore, they reduce arterial blood pressure in animals with renovascular and genetic hypertension, and in transgenic animals over-expressing the renin gene, but have little effect in animals with low-renin hypertension. They are highly selective in that they do not displace ligands that bind to calcium channels or adrenergic, muscarinic, dopaminergic, opioid or neurotensin receptors, and do not antagonise the actions of vasopressin, catecholamines, acetylcholine, serotonin, bradykinin or histamine.

Mechanistically, AII is formed from AI in a reaction catalysed by ACE. AII, being the principal pressor agent of the RAAS, elicits effects that promote hypertension, including vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. AII antagonists such as telmisartan prevent the vasoconstrictor and aldosterone-secreting effects of AII by selectively blocking the binding of AII to the AT1 receptor in the cell membranes of various tissues including vascular smooth muscle and the adrenal gland. This action is therefore dependant upon the pathways of AII synthesis.

AT2 receptors are also present in a wide variety of tissues but they are not known to be associated with cardiovascular homeostasis. In any event, the selectivity of telmisartan comes from its >3000 times greater affinity for AT1 receptors compared with AT2's,

ACEI also block the renin-angiotensin system by inhibiting the biosynthesis of AII from AI, and are widely used in the treatment of hypertension and CHF. ACEI also inhibit the degradation of bradykinin (which is also catalysed by ACE), a property not associated with telmisartan. It is possible that the lack of activity in this respect may make telmisartan less likely to be associated with the side effect of cough that is experienced by some patients taking ACEI.

Blockade of the AT1 receptor inhibits the negative regulatory feedback of AII on renin secretion, but the resulting elevated plasma-renin activity (PRA) and circulating levels of AII do not overcome the effect of telmisartan on blood pressure. It is also pertinent that telmisartan does not bind to, or affect, other receptors or ion channels important in cardiovascular regulation.

In vivo, telmisartan has shown hypotensive activity in the main species used in the toxicology (rat and dog) and in rabbits, cynomolgus monkeys and marmosets. Telmisartan reduced diastolic blood pressure in normotensive rats, dogs and rabbits. In AII-induced hypertension in rats, telmisartan dose-dependently lowered blood pressure after oral, i.v. or i.d. administration, identifying it as a non-competitive receptor antagonist. It also lowered blood pressure in renin-dependent hypertensive rats (in which losartan was 3 times less potent) and in renal hypertensive rats. The effect was long-lasting, particularly in the dog, which appeared to be the more sensitive species. The enduring effect could result from slow dissociation or from slow off-rate of telmisartan from its binding sites. In sodium-depleted normotensive cynomolgus monkeys, telmisartan elicited up to a 42% reduction in MAP without affecting heart rate. Increases in PRA and plasma AII levels suggested that increased PRA maybe a consequence of blocking AII receptors in renin-sensitive tissues. Furthermore, telmisartan inhibited the AII pressor response in anaesthetised marmosets.

Telmisartan also has a cardioprotective function that has been demonstrated in rats. As well as lowering blood pressure in the streptozotocin-induced diabetic rat, it also lowered cholesterol, very low density lipoproteins and triglycerides, and prevented cardiac hypertrophy. In another model, telmisartan improved cardiovascular remodelling associated by the production of e-NOS through PPAR-γ, inhibition of the Rho-kinase pathway and suppression of oxidative stress.

In a series of studies unrelated to its therapeutic activity, telmisartan at very high doses in rats and guinea pigs had some non-specific inotropic activity giving rise to ECG changes, ventricular tachycardia and AV-block with bradycardia; importantly, there were no ECG changes in the comprehensive programme of toxicity studies. In renal function tests in rats, telmisartan had diuretic and natriuretic effects and elevated BUN and creatinine levels; these changes were prevented in animals that were sodium-loaded. It was also reported that telmisartan protects against the nephrotoxic effects of cyclosporin A in minipigs and of diatrizoate in rats. Telmisartan attenuated glitazone-induced increases in body fat mass in genetically obese rats and rats fed a high-fat diet. It did not affect bradykinin-induced bronchoconstriction in anaesthetised guinea pigs. Finally, in CNS studies, telmisartan had no muscle-relaxant activity in mice, and did not affect spontaneous motor activity or hexobarbital sleeping time in rats.

There is no nonclinical information on drug interactions with telmisartan, but clinical data exist in relation to co-administration with digoxin, diuretics, NSAID's, highly protein-bound drugs and drugs that are metabolised by CYP2C19.

Pharmacokinetics

The pharmacokinetics of telmisartan were investigated by the oral and i.v. routes in rats, mice, dogs and rabbits (the main species used in the toxicology). In addition, toxicity studies had complementary toxicokinetics.

Orally administered telmisartan was rapidly absorbed in rats, mice and dogs, but more slowly in rabbits. Absorption was high in rats and mice, with absolute bioavailability of 56-75%. It was lower in dogs though less so when administered after food. In mice and humans, Cmax and AUC were higher in F, but there were no clear gender differences in rats or dogs.

Cmax after an oral dose of 1 mg/kg was similar in rats, dogs and humans, but higher in mice and rabbits. The t½ was reasonably similar in rats, mice and dogs, but was longer in rabbits and humans. In rats, mice and dogs, the compound-related material in plasma was predominantly parent drug whereas, in rabbits, there were roughly equal amounts of parent and metabolite(s). Dose-proportionality with single rising doses was apparent at lower doses in rats and dogs but, at higher doses, it was greater than proportional; similar non-proportionality occurs in humans. In rabbits, plasma concentrations 24 hours after dosing were high, indicating constantly high exposure during repeated daily dosing.

Orally administered telmisartan concentrates predominantly in the plasma fraction of the blood in all species, and correlates with the very high binding to plasma proteins (around 99%). The high degree of binding results in relatively slow metabolism of the parent compound.

Telmisartan is rapidly distributed into a volume of distribution greater than total body water (5.3L/kg in rats, and 1.7-3.0 L/kg in dogs). Tissue distribution studies in rats showed the highest concentration to be in the liver, with lower levels in blood, lung, renal cortex and myocardium; only very low levels were identified in the CNS. In pregnant rats, telmisartan crossed the placenta and was

identified in foetal liver, kidney and lung where, 24 hours after dosing the dam, levels were higher than in maternal blood at that time.

After absorption from the oral route, telmisartan appears predominantly as parent compound (80-90%) in the plasma. It was readily glucuronidated in all microsomal fractions except lung, and its affinity for liver enzymes was greater than those from kidney or small intestine. The rate of metabolism in the liver was slow and drug was retained in the liver, but the rate of elimination of the glucuronide was rapid. The main metabolite in rat and human systems was telmisartan 1-O-acylglucuronide. The metabolism of telmisartan is similar in rats, mice and dogs though, in mice, a glycoside of telmisartan was also identified and accounted for 5-11% of the administered dose.

In all species including humans, telmisartan is preferentially eliminated via the bile into the faeces, with <1% excreted in the urine. There was virtually no enterohepatic recycling of parent drug and only about 10% of the acylglucuronide. In lactating rats, the levels of telmisartan-related material secreted in the milk were about twice those in plasma.

Toxicology

- Single dose toxicity

The single-dose studies provided limited useful information. An oral dose of 2000 mg/kg had no effects in rats, while dogs given 100 mg/kg had white material (presumably drug) in their faeces. Rats dosed i.v. at 200 mg/kg showed depressant effects and, amongst other post-mortem changes, discoloured kidneys and gastric haemorrhage.

- Repeat dose toxicity (with toxicokinetics)

A full regulatory programme of toxicity studies up to 12 months' duration was conducted in rats and dogs. In all repeated dosing studies, there was a commonality of effects in the kidney and gastrointestinal tract, irrespective of whether the drug was administered by gavage, in the diet or intravenously (i.v. studies are not considered in this document). The primary target organs in rats, dogs and mice were kidneys and gastrointestinal tract.

The kidney changes were associated with elevated circulating levels of BUN and creatinine and alterations in electrolyte concentrations. In rats and dogs, there was juxtaglomerular hypertrophy and hyperplasia of the afferent glomerular arterioles; the effects were blocked by sodium loading in rats. They probably arose as a consequence of exaggerated pharmacology; blockade of AII induced inhibition of renin release, thereby stimulating renin-producing cells. Similar changes occur with other sartans and with ACEI, and are considered not relevant to therapeutic doses in patients. Telmisartan was also associated with renal tubular changes in normotensive dogs, which were consistent with hypotension reducing renal perfusion, leading to tubular hypoxia and consequent tubular cellular degeneration and necrosis. In hypertensive patients, the objective of telmisartan treatment would be to restore normal blood pressure; under these circumstances, the hypotensive states necessary for reductions in renal blood pressure and consequent pathology would not arise.

Gastrointestinal erosion and ulceration, and mucosal and submucosal inflammation and subsequent fibrosis, occurred predominantly in rats and rabbits; dogs were less sensitive and mice were not affected. The effects were not a consequence of local irritation because i.v. administration (in studies not reviewed here) gave rise to similar lesions. The precise mechanism is unknown but, like the renal changes, the gut changes can be ameliorated in rats by salt-loading.

There were also consistent anaemic changes (such effects are known to occur with ACEI and AII antagonists as a result of reductions in erythropoietin, presumably due to the decreased influence of AII on the kidney). The effects were generally time- and dose-related in both incidence and severity, and are considered to be a consequence of exaggerated pharmacodynamic activity. They can be prevented by salt-loading in rats.

The decrease in heart weight recorded in most toxicity studies probably reflected a reduction of hypertrophied cardiomyocytes to their normal size, rather than any reduction from the normal. The reduction has been attributed to the absence of trophic effects of AII on growing cardiomyocytes and the prevention of cardiac hypertrophy. There is no loss of contractile function in the smooth muscle cells, so cardiac function is not affected. This is also a class effect with AII antagonists and ACEI.

- Genotoxicity

The recommended range of genotoxicity studies followed accepted protocols and gave uniformly negative results.

- Carcinogenicity

Carcinogenicity studies in rats and mice used high multiples of the maximum human exposure level as justification for setting the highest dose level; furthermore, in rats, it is possible that the MTD was attained. There was no effect on survival, and the toxicological findings were consistent with those in the repeated-dose studies. In both species, statistical analyses of the results revealed no significant positive trend or increase in incidence of neoplasms in any of the telmisartan-treated groups compared with controls. This conclusion was supported by the absence of genotoxicity in a full battery of mutagenicity studies.

- Reproduction Toxicity

Reprotoxicity studies with telmisartan in rats and rabbits followed the conventional Segment I, II and II approach. Complementary toxicokinetics revealed little difference in exposure from non-pregnant rats; there was constant systemic exposure at all doses and dosing periods in both rats and rabbits; furthermore, in rats, drug crosses the placenta and is secreted in the milk of lactating animals. In both species, toxicity was apparent primarily as reductions in food consumption and bodyweight gain. There was no effect on fertility in rats and no evidence of teratogenicity in either species. In weanling rats, a short delay in eye-opening was probably a consequence of reduced bodyweight gain. In rabbits, there was an all-or-nothing effect on intrauterine loss; in some dams, there was total resorption while, in similarly treated animals, foetal development was not affected.

2.4 Clinical Aspects

Introduction

An overview of the clinical pharmacology and a more extensive review of the key clinical trials supporting the established indications for the product have been submitted. A literature search covering the period from the date of publication of the last major review of telmisartan (2006) to the present has been conducted in order to establish that there are no recent reports which might call the efficacy into question. A general overview of the safety is given and is supplemented by a literature search from 2006 to the present to detect any recent ADRs or safety findings which may be of concern. The bioequivalence aspects of the product are considered in detail.

This application is a generic application, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic studies. Then, new clinical studies are neither required nor submitted. The relative oral bioavailability of Telmisartan Teva 80mg tablets and the European brand product Micardis® 80mg tablets (manufactured by Boehringer Ingelheim International GmbH, Germany) was established by comparing the single dose pharmacokinetics of telmisartan from the two formulations, under fasting conditions, in a randomised crossover study.

Exemption

<u>Dissolution profiles of telmisartan</u>

The dissolution profiles of Telmisartan Teva and the reference product have been compared using a discriminatory dissolution test and have been shown to be similar

Justification for biowaiver

The results of the bioequivalence study conducted with the 80 mg tablets could be acceptable for the 20 mg and 40 mg strength because the following criteria for a biowaiver have been fulfilled:

1. The pharmaceutical products are manufactured at the same site by the same manufacturer and manufacturing process.
2. The qualitative composition of the different strengths are the same.
3. The composition of the strengths are quantitatively proportional.

The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20–160 mg, with greater than proportional increases of plasma concentrations (Cmax and Telmisartan 20 mg, 40 mg and 80 mg Tablets AUC) with increasing doses. The selection of the 80mg dose to establish

bioequivalence is in line with the Questions and Answers on the Bioavailability and Bioequivalence guideline EMEA/CHMP/EWP/40326/2006, which indicates that a single strength study may be acceptable provided that the study is conducted on the highest dose for drugs with a demonstrated greater than proportional increase in AUC or Cmax with increasing dose, as is the case with telmisartan. The biowaiver was granted for the lower strengths.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study. No new pharmacodynamic studies and no new therapeutic equivalence studies were submitted.

Pharmacokinetics

- Methods

STUDY DESIGN

This is an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study. Subjects were randomly assigned to one of the two dosing sequences AB or BA under fasting conditions. Each subject received either an 80mg telmisartan generic tablet (Test) or a Micardis® 80mg tablet (Reference), with 240ml water, after an overnight fast, according to a computer generated randomisation list. Following a 14-day washout period, the subjects received the alternative formulation under identical conditions. During each study period, blood samples were taken pre-dose and at 0.125, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.0, 24.0, 48.0 (± 0.5), 72.0 (± 0.5), 96.0 (± 0.5) and 120 (± 0.5) hours after drug administration. Plasma was harvested from these samples and assayed for telmisartan using a validated LC/MS/MS method.

The design employed was considered by the CHMP appropriate for bioequivalence studies. The selection of the 80mg dose to establish bioequivalence is in line with the bioequivalence guideline EMEA/CHMP/EWP/40326/2006, which indicates that a single strength study may be conducted on the highest dose for drugs with a demonstrated greater than proportional increase in AUC or Cmax with increasing dose.

The study was complying with GCP, as claimed by the applicant.

TEST AND REFERENCE PRODUCTS

	Treatment	
	Test (A)	**Reference (B)**
Name:	telmisartan	telmisartan (Micardis®)
Unit dose:	80 mg	80 mg
Regimen:	single dose of 1 x 80 mg tablet per subject in accordance with the randomisation scheme	single dose of 1 x 80 mg tablet per subject in accordance with the randomisation scheme
Lot/Batch No.:	K-36856	706944
Expiry date:	Not available	07 2011
Manufacturing date:	May 23, 2006	Not available
Company Responsible for Manufacturing:		Boehringer Ingelheim International GmbH, Germany

The size of the biobatch was considered acceptable. The Product Certificates of the Test and Reference products were missing but were provided by the applicant during evaluation of the application. It was concluded that tablets used in bioequivalence study have the same pharmaceutical characteristics as the tablets to be marketed.

POPULATION(S) STUDIED

Sixty healthy adult subjects (43 males and 17 females of non-childbearing potential) aged between 20 and 55 years (mean 39 ± 10), with a body mass index (BMI) of between 20.3 and 29.9 (mean 26.1 ± 2.4) and a weight range of 48.7 to 96.9kg (mean 74.3 ± 9.7) participated in the study. A total of 58 subjects completed the study and were included in the pharmacokinetic analysis. The following subjects did not complete the study:

Subject No. 28 withdrew prior to period 2 of the study due to seborrheic dermatitis of the nose.

Subject No. 52 failed to attend for period 2 of the study.

ANALYTICAL METHODS

A HPLC/MS/MS method for the determination of telmisartan was validated according to Bioanalytical Validation Guideline of the FDA.

PHARMACOKINETIC VARIABLES

The pharmacokinetic parameters of interest in this study were: AUC0-t, AUC0-inf, AUCt/inf, Cmax, Residual area, Tmax, Kel and T½ el.

STATISTICAL METHODS

Analysis of Variance (ANOVA) was performed on log-transformed AUC0-t, AUC0-inf and Cmax data. ANOVA was also performed on the untransformed Kel and T½ el data. Wilcoxon's Signed-Rank test was carried out to compare Tmax between treatments. The ratios of least-squares means and 90% geometric confidence intervals were calculated for log-transformed AUC0-t, AUC0-inf and Cmax.. Standard statistical model and industry standard statistical software (SAS) were used.

- Results

Pharmacokinetic Parameters

Parameters		Test (Telmisartan (A)) Mean	SD	CV (%)	Reference (Micardis® (B)) Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	1917.82	1397.89	72.89	1921.13	1322.21	68.82
AUC_{0-inf}*	(ng·h/mL)	2085.11	1498.08	71.85	2086.25	1452.07	69.60
$AUC_{t/inf}$*	(%)	93.35	7.45	7.99	93.06	7.55	8.12
C_{max}	(ng/mL)	323.06	408.53	126.46	297.47	282.36	94.92
Residual area*	(%)	6.65	7.45	112.09	6.94	7.55	108.91
T_{max}	(h)	1.36	1.05	76.74	1.26	1.13	89.91
T_{max}**	(h)	1.00	0.50	-	0.750	0.500	-
K_{el}*	(h^{-1})	0.0284	0.0121	42.39	0.0293	0.0125	42.49
$T_{½ el}$*	(h)	29.83	19.17	64.27	30.46	21.58	70.85

*For these parameters, N = 57.

**Medians and interquartile ranges are presented.

Telmisartan (A) vs Micardis® (B)

	AUC_{0-t}	AUC_{0-inf}*	C_{max}
Ratio[1]	97.73%	98.44%	101.43%
90 % Geometric C.I.[2]	92.92% to 102.78%	93.04% to 104.14%	90.85% to 113.23%
Intra-Subject CV	16.07 %	17.89 %	35.96 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Telmisartan (A)} - \text{Micardis® (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

*For this parameter, N = 57

- Conclusions

This study confirms that the test product (Telmisartan Teva 80mg tablets) is bioequivalent to the Reference formulation (Micardis® 80mg tablets, manufactured by Boehringer Ingelheim International GmbH, Germany) with respect to rate and extent of availability.

The study was conducted according to Good Clinical Practice. The analytical validation reports are compliant with regulatory requirements.

The design employed was appropriate for bioequivalence studies. A single dose study is considered appropriate in view of the fact that telmisartan does not accumulate during repeated administration

The residual area was 6.65% for the test product and 6.94% for the reference product, indicating that the pharmacokinetic time points were adequate to detect 80% of the AUC to infinity, for both products.

The 90% geometric confidence intervals of the ratio (Test/Reference) of least-squares means of the log transformed data were within the internationally accepted range of 80% and 125% for AUC0-t and for Cmax as well.

Pharmacodynamics

No new data were required and provided by the Applicant.

Post marketing experience

The product has not been marketed until now therefore no post-marketing experience could be gathered.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for Telmisartan Teva should follow the PSUR submission schedule for the reference medicinal product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant Version 6, November 2008 fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

No description of Risk Management plan has been provided by the applicant. Since the application concerns a generic with a reference medicinal product for which no safety concerns requiring additional risk management activities have been identified this approach is considered acceptable.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical, and clinical information and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Recommendation

Based on the CHMP review of available data, the CHMP considered that the benefit/risk ratio of Telmisartan Teva in the treatment of essential hypertension in adults was favourable and therefore recommended the granting of the marketing authorisation.